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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	18

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/743,690	Applicant(s) CHRISTELLER ET AL.	
	Examin r Anne R. Kubelik	Art Unit 1638	

-- The MAILING DATE f this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-23,31 and 53-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-23,31 and 53-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims1-15, 24-30 and 32-52 have been cancelled, claims 16-23, 31 and 53-54 have been amended, and claims 55-64 have been added, as requested in Paper No. 17, filed 23 May 2003. Claim 24 could not be amended because it was cancelled. Claims 16-23, 31 and 53-64 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

3. The objection to claim16-21, 23, 31 and 53-54 because of informalities is WITHDRAWN in light of amendments to the claims,

4. The rejection of claim 54 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is WITHDRAWN in light of amendment to the claim.

5. The rejection of claims 16-23, 31 and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boller et al (US Patent 6,054,637, filed June, 1991) in view of Hilder et al (1987, Nature 330:160-163), taken with the evidence of Applicant's admission is WITHDRAWN in light of amendment to the claims to limit the invention to biotin binding sequences.

Response to Argument

6. The rejection of claims 16-23, 31 and 53-54 under 35 U.S.C. 103(a) as being unpatentable over Raikel (1994, US Patent 5,360,726) in view of Czapla et al (WO 94/00992) is WITHDRAWN in light of Applicant's arguments.

Claim Rejections - 35 USC § 112

7. Claims 16-23, 31 and 53-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 19 November 2002, as applied to claims 16-23, 31 and 53-54, due to amendment of the claims. Applicant's arguments filed 23 May 2003 have been fully considered but they are not persuasive.

As explained in the 112, 2nd, rejection below, claim 1, as written, is drawn to nucleic acid comprising a biotin-binding sequence, which implies that the nucleic acid itself binds biotin. This rejection is also written assuming that Applicant intended the nucleic acid encodes a protein that binds biotin. Similarly, claim 1, as written, is drawn to nucleic acid comprising a vacuole targeting sequence, which implies that the nucleic acid itself targets the vacuole.

The claims are broadly drawn to nucleic acids that encode a chimeric protein comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, or nucleic acids comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, cells and plants transformed with those nucleic acids, and methods of using the cells and plants to produce the protein. In contrast, the specification only describes vectors encoding the potato proteinase inhibitor I signal peptide operably linked to avidin mature peptide or potato proteinase inhibitor II signal peptide operably linked to streptavidin. Applicant does not describe other DNA

molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described nucleic acids that encode a chimeric protein comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, within the full scope of the claims or nucleic acids comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, at all, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding

> human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

Applicant urges that the specification adequately defines the terms such that the claims are not indefinite under 35 U.S.C. 112, second paragraph and that the specification has been amended to recite that the plant-noxious pest control sequence is a biotin-binding sequence. Applicant urges that the specification provides examples of multiple vacuole targeting sequences (response pg 7-8).

This is not found persuasive because the specification does not describe nucleic acids that encode functional variants or fragments of biotin-binding sequences, or nucleic acids that are vacuole targeting sequences or biotin-binding sequences, or functional variants or fragments thereof.

8. Claims 16-23, 31 and 53-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids that encode a chimeric protein comprising any vacuole targeting sequence operably linked to avidin or streptavidin, cells and plants transformed with those nucleic acids, and methods of using the cells and plants to produce the protein, does not reasonably provide enablement for nucleic acids that encode a chimeric protein comprising any vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof or nucleic acids comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, cells and plants transformed with those nucleic acids, and methods of using the cells and plants to produce the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection

set forth in the Office action mailed 19 November 2002, as applied to claims 16-23, 31 and 53-54, due to amendment of the claims. Applicant's arguments filed 23 May 2003 have been fully considered but they are not persuasive.

As explained in the 112, 2nd, rejection below, claim 1, as written, is drawn to nucleic acid comprising a biotin-binding sequence, which implies that the nucleic acid itself binds biotin. This rejection is also written assuming that Applicant intended the nucleic acid encodes a protein that binds biotin. Similarly, claim 1, as written, is drawn to nucleic acid comprising a vacuole targeting sequence, which implies that the nucleic acid itself targets the vacuole.

The claims are broadly drawn to nucleic acids that encode a chimeric protein comprising any vacuole targeting sequence operably linked to any biotin binding sequence or a variant or fragment thereof, or nucleic acids comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, cells and plants transformed with those nucleic acids, and methods of using the cells and plants to produce the protein.

The instant specification, however, only provides guidance for vectors encoding the potato proteinase inhibitor I signal peptide operably linked to avidin mature peptide (example 2) or potato proteinase inhibitor II signal peptide operably linked to streptavidin (example 3); immunodetection of avidin in transformed tobacco (examples 4-5); analysis of the toxicity of the avidin- or streptavidin-transformed tobacco plants to a variety of larvae, including potato tuber moth larvae, common cutworm, and cotton bollworm, (examples 6-9); toxicity of purified streptavidin and/or avidin proteins to pine shoot tip moth larvae, neonate clover root weevil, or neonate argentine stem weevil (examples 10 and 13), avidin-painted leaves to neonate willow

sawfly larvae or black field cricket (examples 11-12), and a demonstration that adult clover root weevils, honeybees, slugs, snails and root-knot nematodes were not harmed by a diet that contained avidin, avidin-painted leaves or transgenic leaves (examples 14-17); and toxicity of protease inhibitor or Bt toxin-painted avidin transformed tobacco leaves to *Helicoverpa armigera* (example 18).

The instant specification fails to provide guidance for nucleic acid that bind biotin, for variants or fragments thereof, for nucleic acids encoding biotin-binding proteins other than avidin or streptavidin, or for a variant or fragment thereof, or plants transformed with those nucleic acids.

Making substitutions in proteins is not predictable. Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding variants of biotin binding proteins. Making all possible single amino acid substitutions in an 128 amino acid long protein like avidin would require making and analyzing 19^{128} nucleic acids, and making all possible single amino acid substitutions in an 184 amino acid long protein like streptavidin would require making and analyzing 19^{184} nucleic acids. Thus, without guidance making variants is not straightforward.

As the specification does not describe the transformation of any plant with a nucleic acid that encodes a chimeric protein comprising any vacuole targeting sequence operably linked to any biotin-binding sequence other than avidin or streptavidin, or functional variants or fragments thereof, or nucleic acids comprising a vacuole targeting sequence operably linked to any biotin-binding sequence, or functional variants or fragments thereof, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those that control plant pests, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that claims are enabled if one of skill in the art could use the specification to make and use the invention without undue experimentation. Applicant urges that the specification provides examples of multiple vacuole targeting sequences, vectors and host cells, methods for plant transformation, and plants that are transformed. Applicant thus urges that undue experimentation is not required (response pg 8-9).

This is not found persuasive because the specification does not teach nucleic acids that encode functional variants or fragments of biotin-binding sequences, or nucleic acids that are vacuole targeting sequences or biotin-binding sequences, or functional variants or fragments thereof.

9. Claims 16-23, 31 and 53-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that

Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is different from the rejection set forth in the Office action mailed 19 November 2002, as applied to claims 16-23, 31 and 53-54, due to amendment of the claims. Applicant's arguments filed 23 May 2003 have been fully considered but they do not apply to these new rejections.

Claim 16 is indefinite for its recitation of "nucleic acid molecule comprising ... a vacuole targeting sequence; and ... a biotin binding sequence." It is not clear if Applicant intended that the nucleic acid itself bind biotin or if applicant intended that the nucleic acid encode a protein that binds biotin. Similarly, it is not clear if Applicant intended that the vacuole targeting sequence (a nucleic acid) itself target vacuoles or if applicant intended that the nucleic acid encode a protein that targets vacuoles. Dependent claims should be amended accordingly.

Claim 16 is indefinite for its recitation of "functionally equivalent variant". It is unclear what function is equivalent, and it is unclear how the sequence of the variant differs from that of the biotin binding sequence.

Claim 16 is indefinite for its recitation of "fragment thereof". It is unclear if the fragment is of the variant or the biotin binding sequence or if the fragment binds biotin.

Claim 21 lacks antecedent basis for the limitation "the polypeptide according to claim 16" as claim 16 is drawn to a nucleic acid molecule.

Claim 22 lacks antecedent basis for the limitation "The method for producing a pest resistant plant".

Claim 31 lacks antecedent basis for the limitation "the chimeric polypeptide according to claim 16" as claim 16 is drawn to a nucleic acid molecule.

Claims 55-56 and 59 lack antecedent basis for the limitation "The nucleic acid of claim 16" as claim 16 is drawn to a nucleic acid molecule. Dependent claims should be amended accordingly.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The Official fax phone number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
August 5, 2003

AMY J. NELSON, PH.D
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